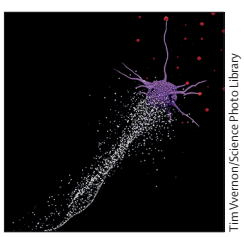
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Stimulating severe COVID-19: the potential role of GM-CSF antagonism



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Over the past 20 months of the COVID-19 pandemic, a great deal has been crystallised about the ideal therapeutic targets for infected patients. For very sick patients who require hospitalisation, we now know that targeting the dysregulated host response is of greater value than targeting the virus. Through steroids, interleukin(IL)-6 blockade, IL-1 blockade, tyrosine kinase inhibition, or Janus kinase inhibition, we have a breadth of clinical trials that show the possible mortality benefits of both broad and focused immunomodulation in severely ill patients with COVID-19. As the pandemic continues, there is a need to understand whether combinations or different agents that target alternative pathways would continue to improve clinical outcomes, or whether there are ways of identifying specific patients with a higher likelihood of benefit from specific therapies.

One of the key components of the detrimental hyperinflammatory response in COVID-19 is granulocyte-macrophage colony-stimulating factor (GM-CSF), which is an immunomodulatory cytokine that might help to clear respiratory microbes by stimulating alveolar macrophages, but when in excess can cause damage. Its concentrations are low or undetectable in healthy individuals, yet many conditions can cause a rapid increase its concentration.[1] Increased circulating concentrations of GM-CSF have been described in patients with COVID-19 compared with healthy controls.[2] In the later stages of lung disease in COVID-19, excessive GM-CSF production can contribute to the dysregulated immune response in severe COVID-19,[3] in which, upstream of IL-1 and IL-6, activated T cells target neutrophils and macrophages.[4] Agents that interfere with its actions have high plausibility for benefit, not just in COVID-19, but in other acute inflammatory conditions, such as acute respiratory distress syndrome or sepsis.[5]

In *The Lancet Respiratory Medicine*, Zelalem Temesgen and colleagues[6] report on a multicentre, placebo-controlled clinical trial of hospitalised patients with COVID-19, showing that lenzilumab, a neutralising monoclonal antibody against GM-CSF, is associated with improved survival without invasive mechanical ventilation at 28 days. Lenzilumab is a monoclonal antibody that directly binds GM-CSF and is being tested for conditions such as chronic myelomonocytic leukaemia and B-cell lymphoma.

Of 520 randomly assigned patients who were hypoxic or who required oxygen, but who did not require invasive mechanical ventilation, 479 patients were included in the modified intention-to-treat analysis. Patients in the lenzilumab group showed a 6% absolute increase in survival without ventilation at 28 days compared with the placebo group (198 [84%] of 236 patients *vs* 190 [78%] of 243 patients; hazard ratio [HR] 1·54 [95% CI 1·02–2·32], p=0·040). This difference on the outcome of survival without ventilation was primarily driven by more patients in the placebo group requiring invasive ventilation (49 [20%] patients) than those in the lenzilumab group (26 [11%] patients; HR 0·52 [0·32–0·82], p=0·0059). Key secondary outcomes, such as mortality, ventilator-free days, intensive care unit days, or recovery time, along with adverse events were not significantly different between the two groups.

This study population had lower baseline C-reactive protein (CRP) concentrations than the cohorts in RECOVERY and REMAP-CAP—trials where IL-6-targeted therapy has shown the largest benefit.[7,8] Exploratory sensitivity analyses suggested greater benefit of lenzilumab in patients with CRP concentrations less than the median value of 79 mg/L; further study of a CRP-guided approach, possibly targeting patients with lower CRP concentrations, earlier in their disease course, or of a different disease phenotype, could therefore be warranted. Whether biomarker-driven immunotherapy with stratification of patients can guide individualised use of immunomodulatory treatments in COVID-19 needs to be explored.

Studies of other agents acting to block GM-CSF in COVID-19 are also starting to report results. Otilimab (another GM-CSF inhibitor) is being studied in an older cohort of patients, aged more than 70 years, after some encouraging results in a subgroup of an initial study.[9] Small studies of mavrilimumab (a GM-CSF receptor inhibitor) have shown no benefit,[10] although larger studies are also underway. For lenzilumab, further study

is happening through the ACTIV-5 platform, given the encouraging results from this trial.

As background standard of care for severe COVID-19 rapidly evolves, doing clinical trials of targeted immunomodulators becomes increasingly difficult. This trial, which enrolled patients between May, 2020, and January, 2021, did not allow administration of other immunomodulators, such as tocilizumab or baricitinib, during the acute stay, and was done before these medications became more routinely used in clinical practice. Without knowledge of the added benefit or the added risk of different, concurrently used immunomodulators, trials that do not integrate available standards of care are difficult to interpret. Hence, the specific value of GM-CSF blockade, in the absence of comparative or additive data with other targeted immunomodulators, is impossible to evaluate. As treatment regimens for COVID-19 constantly change and become more complex, evaluation of interactions must be the goal, and probably requires coordination across clinical trials, industry sponsors, and the involvement of large platform trials.

We declare no competing interests.

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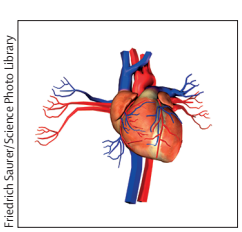
The heart of the matter: modulating therapeutic effects of adrenomedullin in cardiogenic shock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The pathophysiological model for cardiogenic shock was first described by Hollenberg and colleagues,[1] in which severely depressed myocardial contractility, due to acute coronary thrombosis, initiates progressive worsening of systolic and diastolic dysfunction. These impairments result in systemic hypoperfusion, coronary ischaemia, increased ventricular filling pressures, multiorgan system failure, and death.[1] A key premise to this paradigm has been the maladaptive role that systemic vasoconstriction (a compensatory response to reduced cardiac output) has in perpetuating this cascade through its adverse effects on afterload and myocardial oxygen demand.[2] However, early subanalyses of the Should We Emergently Revascularise Occluded Arteries in Cardiogenic Shock (SHOCK) trial further informed our understanding of the mechanisms of shock, in which 18% of patients with cardiogenic shock due to acute myocardial infarction also developed a concomitant systemic inflammatory response syndrome (SIRS).[3] Often characterised by refractory and non-sepsis related vasoplegia, SIRS condition has been reported in up to 25% of patients with acute myocardial infarction without cardiogenic shock following percutaneous revascularisation and is independently associated with increased risk for 90-day mortality.[4] An analysis of 8995 individuals admitted to the cardiac intensive care unit showed a higher prevalence of SIRS in cardiogenic shock, with nearly one in three patients having met the syndrome's criteria. Additionally, its presence was associated with increased risk for in-hospital and 1-year mortality across the severity spectrum of cardiogenic shock, as